

### **REMARKS**

Claims 81- 87 are pending. Claims 1-65 and 80 are cancelled as the result of a restriction requirement, and without prejudice to the prosecution of their subject matter in other patent applications. Claims 66-79 are cancelled to focus the prosecution of the application and without prejudice to the prosecution of their subject matter in other patent applications. Claims 81 - 87 are added to more particularly state Applicants' invention. Although support for the new claims may be found throughout the specification, (i) new claim 81 is particularly supported by paragraphs 8, 11, 24, 123, 130-138, 164; (ii) new claims 82 and 86 are particularly supported by paragraph 26; (iii) new claims 83 and 87 are particularly supported by paragraphs 102 and 144; (iv) new claim 84 is particularly supported by paragraph 121; and (v) new claim 85 is particularly supported by paragraphs 8, 11, 24, 123, 130-135, and 169. None of the new claims constitute new matter.

Applicants acknowledge the Examiner's clarification that the restriction requirement included a species election, where the elected species includes methods comprising contacting cells with Sonic Hedgehog ("SHh") protein.

The claims are rejected as indefinite, not enabled, and as obvious over the art. For reasons set forth below, it is requested that all rejections be removed and that the claims be allowed to issue.

#### **1. The Claims Are Not Indefinite**

Claims 66-79 are rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim that subject matter which Applicants regard as their invention. In particular, the rejection is based upon the following.

First, the Examiner objects that there is insufficient antecedent basis for reference, is step (e) of claims 66 and 77, to “the candidate modulator in step (b)”.

New claim 81 provides a proper antecedent basis for referring to a modulator added in an earlier step.

Second, the Examiner objects that there is not a proper basis for comparing the cells in steps (b) and (c) of claims 66 and 77.

New claim 81 provides a proper basis for comparison.

Third, the Examiner contends that claims 78 and 79 are incomplete for omitting essential steps, for example a correlation step.

The new claims are believed, by Applicants, to contain all essential steps.

For all the foregoing reasons, the rejections for indefiniteness should be removed and not be reapplied to the new claims.

## **2. The Claims Are Enabled**

Claims 66-79 are rejected under 35 U.S.C. §112 as unenabled because, according to the Examiner, the specification, while being enabling for methods of activating Hh signalling using an Hh protein, are not enabling for methods involving any other substance. The Examiner states that the activators of Hh signalling listed in the specification extends to “signalling molecules that are not specific to Hh signalling” and that “[f]urther experimentation would be required to determine if the test compound actually modulates an Hh signalling pathway.” The Examiner states that “[b]y encouraging the skilled artisan to employ molecules that are only coincidentally related to Hh signaling, the specification actually guides the skilled artisan away from identifying a modulator of an Hh signaling pathway.”

Applicants respectfully disagree with the Examiner's position that the specification is not enabling because it provides a broad definition for activators of an Hh signalling pathway. Paragraph 69 of the specification states "[a]n 'activator' of a hedgehog signalling pathway includes a factor that effects, increases, induces, initiates, or stimulates signalling within a hedgehog signalling pathway." Applicants assert that this would be considered an appropriate definition by the person skilled in the art, and as supportive evidence, invite the Examiner's attention to Exhibit A, "Targeting the Hedgehog Signaling Pathway with Small Molecules" by Kiselyov, 2006, Anti-Cancer Agents Med. Chem. 6:445-449.

Therefore, the full scope of a definition of agents that directly or indirectly activate hedgehog signalling is enabled. Nevertheless, in order to advance prosecution of this application, Applicants have amended the claims to provide for use of "a factor that directly effects signaling within a Hh signalling pathway", without prejudice to the prosecution of claims covering indirect Hh signalling activation in other patent applications. Accordingly, the rejection should be removed and not reapplied to the new claims.

### **3. The Claims Are Not Obvious**

Claims 66-79 are rejected under 35 U.S.C. §103(a) as obvious over United States Patent No. 5,844,079 by Ingham et al. ("Ingham"), in view of United States Patent Application Publication No. 20020151056 by Sasai et al. ("Sasai"), United States Patent Application Publication No. 20040092012 by Okano et al. ("Okano" and United States Patent No. 6,833,269 by Carpenter ("Carpenter").

According to the Examiner, (i) Ingham discloses contacting stem cells with a hedgehog polypeptide to induce motor neuron differentiation and that such cells may be used in

assays to identify neurotrophic factors; (ii) Sasai teaches differentiation of embryonic stem cells into neural ectoderm by contacting cells with SHh; (iii) Okano discloses contacting embryonic stem cells with SHh to produce motor neurons and GABAergic neurons; and (iv) Carpenter teaches contacting embryonic stem cells with SHh and methods for making neural cells from embryonic stem cells.

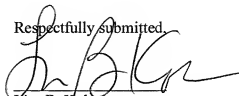
The basis for this rejection is obviated by the cancellation of claims 66-79 and their replacement with claims 81-87, all of which relate to the use of a combination of retinoic acid and an activator of Hedgehog signalling to produce motor neuron differentiation.

Indeed, the discovery that the combination of retinoic acid and hedgehog agonist could induce embryonic stem cells to differentiate into motor neurons which, transplanted into an embryo, could successfully integrate into the spinal cord and extend processes to their muscle targets was hailed as an exciting discovery when first published in Wichterle et al., 2002, *Cell* 110:385-397 (“Wichterle”, published after the priority application of the instant application was filed). A copy of Wichterle is attached as Exhibit B, together with a copy of a news release by the prestigious Howard Hughes Medical Institute (Exhibit C), inventor Jessell being a Howard Hughes Medical Institute Investigator, which puts the magnitude of the discovery in context. The subject matter of Wichterle is found in the working examples of the instant application, and the critical aspects of the discovery are embodied in new claims 81-87. Applicants assert that the invention, as presently claimed, is not obvious over the cited art, either any of the cited references taken individually or in any combination. Accordingly, the rejection should be removed and not reapplied to the new claims.

4. **CONCLUSION**

For all the foregoing reasons, the new claims are in condition for allowance and the rejections should be removed and not reapplied.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'L. B. Kole', written over a horizontal line.

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